

Origins of the Obstetric and Gynaecological Syndromes

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Abstract

For many decades (1945–2011) narrowed, uterine arterioles were thought to be the histological hallmark of preeclampsia after their original description by AT Hertig, Harvard, MA, in 1945. More recently Professors Brosens & Romero, described narrowed, uterine arterioles in many of the “great” obstetric syndromes including preterm labour, placental abruption, foetal growth restriction, pre-eclampsia, etc. In unrelated studies, our group have found narrowed arterioles surrounded by “halos” of injured nerves in the uterus, and other pelvic organs, in many of the gynaecological syndromes including chronic pelvic pain, endometriosis, “painful” adenomyosis, vulval pain, interstitial cystitis, etc.

Keywords: Autonomic nerves, Obstetric syndromes, Gynaecological syndromes, Difficult first labours, Straining on the toilet, Denervation, Reinnervation

Condensation

Many obstetric and gynaecological syndromes result from preventable injuries to pelvic autonomic nerves sustained during “difficult” first labours, minor gynaecological surgery, and, straining on the toilet.

Introduction

Reviewing historic reports of the obstetric syndromes there is clear evidence of partial or complete, single or multi-layered, “halos” of empty, nerve sheaths around narrowed arterioles in the placental bed though these histological features have not been previously discussed or analysed. Traumatic injuries to autonomic nerves release cytokines and growth factors with the dual effects of (i) regeneration of injured nerve fibres and, (ii) medial hyperplasia (“narrowing”) of the adjacent, denervated arterioles. Common causes of neuropathic injury in the female pelvis include [1] “difficult” primigravid labours (prolonged >12 hours, or, complex), [2] some forms of “neuropathic” gynaecologic surgery, and [3], coordinate, and, incoordinate, physical efforts during defaecation.

We propose that many obstetric and gynaecological syndromes originate from injuries to pelvic autonomic nerves leaving characteristic histological signatures of (i) narrowed arterioles surrounded by “halos” of injured nerves in the gynaecological syndromes, and, (ii) narrowed arterioles surrounded by “halos” of injured nerve sheaths in the obstetric syndromes.

For many decades (1945–2011), narrowed uterine arterioles in the placental bed were held to be the characteristic injury in pre-eclampsia [1–5]. More recently, Professors Brosens and Romero found that narrowed, uterine arterioles were characteristic of many of the “great” obstetric syndromes (**Figures 1A and 1B**), and in their account, attributed them to “defective placentation” [6]. Independent, and unrelated, studies by our group found evidence of narrowed arterioles (**Figures 1A and 1B**), together with “halos” of injured autonomic nerves, in many of the gynaecological syndromes e.g. “endometriosis”, different patterns of adenomyosis, interstitial cystitis, vulval pain, etc. [7] (**Figures 2 and 3**). Reviewing historical papers in preeclampsia between 1945 and 1972 reveals many illustrations of narrowed, uterine arterioles in the placental bed with complete or incomplete, single or multi-layered, “halos” of empty nerve sheaths that have neither attracted comment, nor analysis [1–5], (**Figures 1A and 1B**). In AT Hertig’s original paper there is some evidence of a partial “halo” of empty cells around narrowed arterioles though accounts by later authors including Zeek & Assali, Dixon & Robertson, and, Brosens & Pijnenborg include

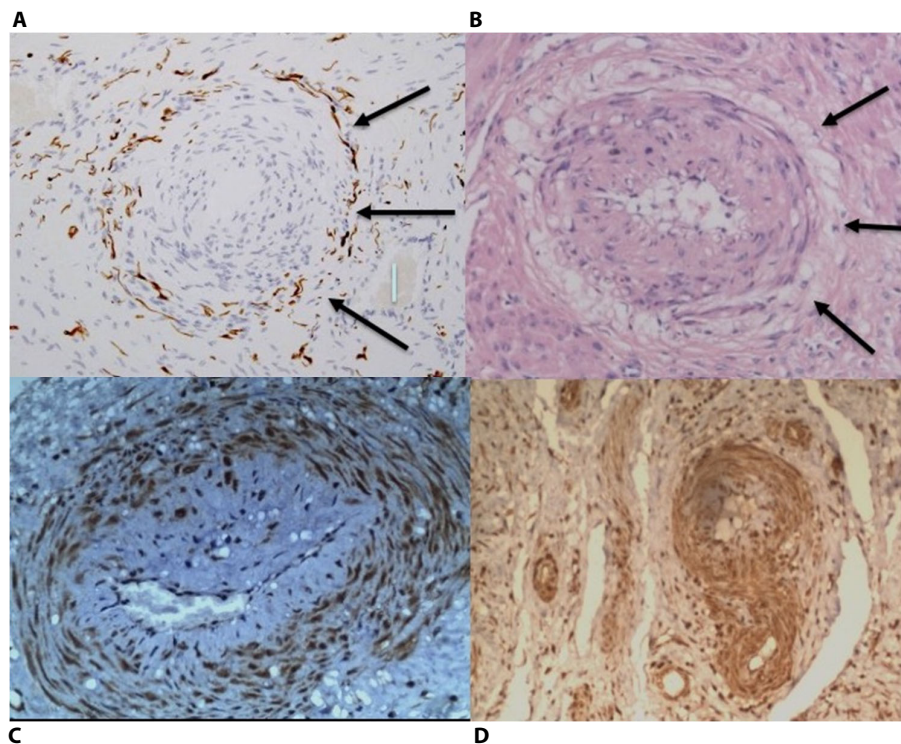


Figure 1. Common histological origins of the obstetric and gynaecological syndromes. A-B. Narrowed, uterine arterioles in gynaecological (A) (x100, anti-S100) and obstetrics (B) (x100, haematoxylin and eosin) syndromes, result from injuries to “mixed”, autonomic nerve bundles. In painful gynaecological syndromes there are “halos of injured nerves around narrowed arterioles” (A, arrowed) whereas in the obstetric syndromes there are “halos of empty, injured, nerve sheaths”. “Halos” of empty, injured nerve sheaths (B, arrowed) are illustrated in many historical reports of pregnant uteri (B,C,E,F) though have not attracted comment, discussion or analysis [1–5]. C. Narrowed uterine arteriole (x100, anti-P2X3, brown) in preeclampsia expressing specialized, purinergic, P2X3, “stretch” receptors that may represent the afferent mechanism in the early-onset (<34 weeks) preeclampsia syndromes. P2X3 receptor proteins are expressed in the maternal chorion during normal pregnancy and may play a role in the onset of labour [53,54]. D. Expression of specialized, purinergic, P2X3, “stretch” receptors in myometrium (x100, anti-P2X3, brown) in the “late-onset” (>34 weeks) preeclampsia syndromes.

many more illustrations of “halos” of injured nerve sheaths in their respective accounts [1–5].

Injuries to autonomic nerves release cytokines and growth factors that have the dual effects of (i) relentless, regeneration of injured nerves, (ii) hyperplasia of the denervated tunica media leading to narrowing of adjacent arterioles [8]. Narrowed uterine arterioles (9, vessel:lumen diameter > 1.4) are frequently surrounded by “halos of injured nerves” in gynaecological syndromes (Figures 1A and 2d) and undiscussed, “halos” of injured nerve sheaths in the pregnant uterus [1–5], (Figure 1A). Any injury to an autonomic nerve (denervation) result in regeneration of injured nerves (reinnervation), with largely-unknown biological characteristics, from the proximal stump [8]. They have unpredictable, clinical consequences that produce wide-ranging, gynaecological symptoms and presentations over varying periods of time (3-10 years, Table 1)). Variable, latent periods between initial neurological injuries and subsequent, diverse, clinical presentations vary with the nature of the injury, tissue of origin, the

neurapraxis effects of intervening pregnancies, etc., and, may have obscured their etiological origins. These unstudied, regenerating nerves continue to proliferate causing recurrent, painful symptoms that may become apparent in a woman’s postmenopausal years despite prior hysterectomy and her menopause. The obstetric syndromes largely result from the consequences of pre-pregnancy injuries to uterine nerves rather than an early pregnancy process (8-18 weeks) such as “defective placentation” as suggested by Brosens and Romero [6]. These common origins may explain some of the many, clinical associations between the obstetric and gynaecological syndromes e.g. endometriosis and intrauterine growth retardation [10], or, adenomyosis and preterm labour [11].

Pelvic Autonomic Nerves (Figures 2 and 3)

In the post-1945 era, many medical schools changed their embalming agents from alcohol to formalin to prolong the teaching life of cadavers; formalin selectively destroys autonomic nerves [12], (Figure 3). As a consequence, many

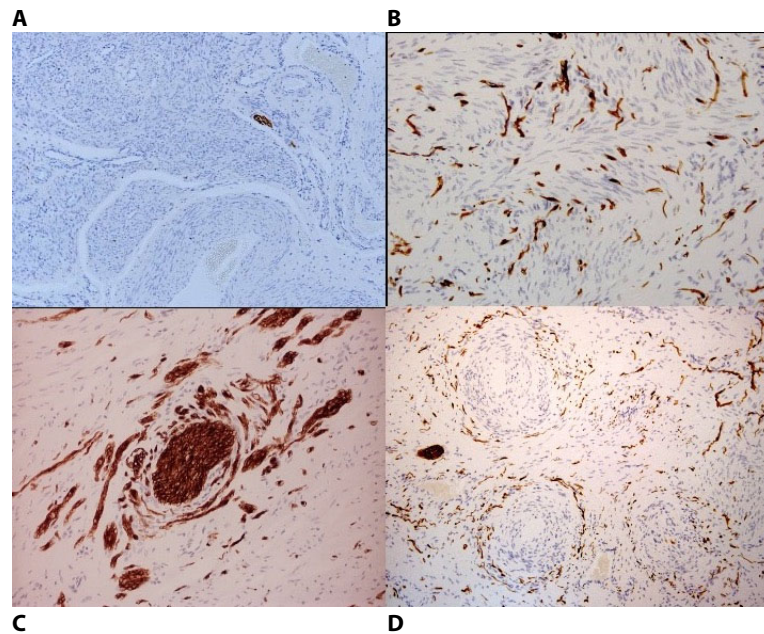


Figure 2. Different patterns of neuropathic injury in the uterus (A-D). **A.** The normal, endometrial-myometrial nerve plexus separates endometrium from myometrium. It is vulnerable during evacuation of the uterus. **B.** Aberrant reinnervation in uterine stroma associated with traumatic injury to “mixed” uterine nerve bundles [19]. **C.** “Collateral sprouting” of uterine nerve bundles that is pathognomonic for prior traumatic injury [19]. **D.** Perivascular nerve fibre proliferation (PVNFP) around narrowed arterioles associated with prolonged physical efforts during defaecation, or, prolonged maternal, voluntary efforts in the second stages of labour [19,23].

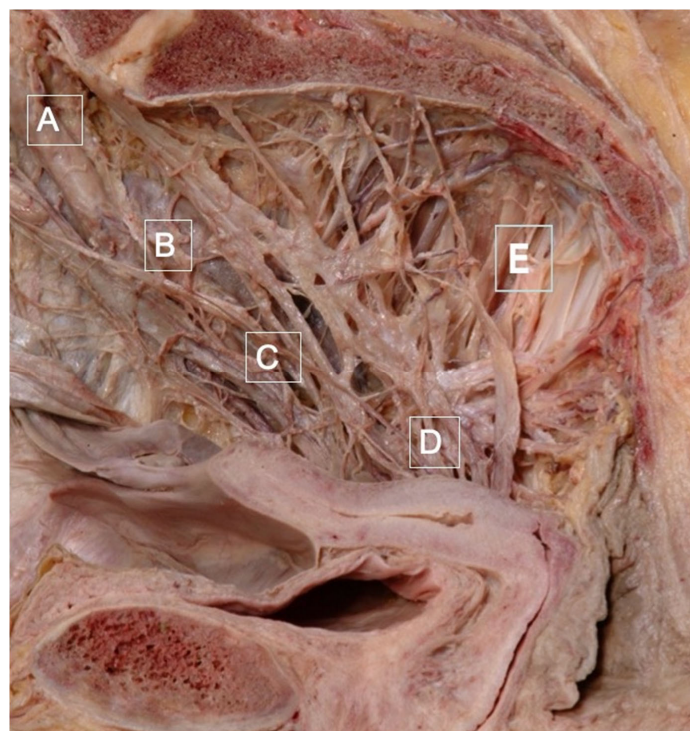


Figure 3. The full morphology of the pelvic autonomic nerves. **(A)** Superior hypogastric nerve plexus, **(B)** hypogastric nerve, **(C)** inferior hypogastric nerve plexus, **(D)** uterovaginal nerve plexus, **(E)** pelvic parasympathetic nerves (S2-4).

contemporary physicians have not seen the full morphology of the cardiac, coeliac and pelvic autonomic plexi, and, are unfamiliar with their pelvic neuroanatomy. In the female pelvis, two bundles of uterine and tubal nerves from sympathetic segments T10-L2 and parasympathetic segments S2-4, pass through (i) the central neurovascular bundle of the uterosacral ligaments, and, (ii) with the uterine vessels to supply the uterus, cervix and Fallopian tubes [13,14], (**Figure 3**). Most viscera carry similar submucosal and subserosal plexi that may be important during embryogenesis. The nerves in the uterosacral ligaments supply the inner layers of the three target organs (uterus, cervix and fallopian tube) including the endometrial-myometrial nerve plexus [14], inner concentric layer of nerves in the cervix [14], and, the inner layer of the proximal four-fifths of the fallopian tubes [15,16]. Injuries to the uterosacral ligaments may be visible as avulsion, scarring, thinning or thickening, with direct consequences for their contained nerves that supply the submucosal layers of the uterus and fallopian tubes (**Figures 4A–4F**). Reinnervation in the insertions of the uterosacral ligament may be a frequent contributory source of chronic pelvic pain [15], (**Figure 2B**). Nerve bundles passing with the uterine vessels supply the uterine subserosal, outer, concentric layer of the cervical plexi, and, outer layers of the proximal four fifths of the fallopian tube [13]. Injuries to these nerves often result in ampullary ectopic pregnancy or hydrosalpinx [16]; the fimbriae receive a dense innervation from the ovarian plexus via the mesosalpinx [17].

Krantz described important subserosal (lateral) and endometrial-myometrial nerve (medial) nerve plexi in the uterus; the latter being vulnerable to uterine curettage [14] whereas the cervix contains two concentric layers of “mixed” autonomic nerve bundles in 12-16 individual bundles that may be at risk during dilatation and curettage, and other minor surgical procedures [14]. Applying a multi-toothed vulsellum to the anterior lip of the cervix may injure both layers of concentric nerves creating the conditions for a dense field of regenerating, injured nerves with subsequent, “painful” hysteroscopy or difficult, IUCD insertion after a latent period of approximately three years [18]. Applying excessive traction to the cervix may avulse both the uterosacral bundle of nerves (“uterosacral nerves”), and, the second bundle of nerves running with the uterine vessels ([14], “uterine nerves”) with potentially-significant impacts on a woman’s fertility [19]. The endometrial-myometrial nerve plexus (of Krantz, [14]) is clearly vulnerable to over-vigorous, uterine curettage that may also contribute to the development of some forms of adenomyosis (**Figure 1A**). Clinicians should be aware of the detailed neuroanatomy of the lower genital tract and potential “neuropathic” consequences of intrapartum and gynaecological surgical procedures.

Causes of Injuries to Pelvic Autonomic Nerves

Common injuries to pelvic autonomic nerves result from (i) “difficult” first labours, (ii) straining on the toilet, and, (iii)

some forms of “neuropathic” gynaecological surgery [19]. Evidence for the gynaecological outcomes of “difficult” first labours emerge from 2,240 primigravid women followed up for 47 months in the Avon Longitudinal Study of Parents and Children (20, ALSPAC, 1992). Prolonged (>12 hours) and “complex” (induction of labour, foetal macrosomia >4000 g, persistent occipito-posterior presentations, forceps delivery) deliveries doubled the risk of severe gynaecological symptoms (chronic pelvic pain and heavy menstrual bleeding) at 47 months postpartum [20]. Attrition of the dataset did not permit potential differences in hysterectomy rates at 10 years postpartum to be evaluated which may have provided definitive, prospective information regarding the important, though long term, consequences of these injuries.

Processed diets promote low residue stools that are difficult to evacuate [21,22]. Prolonged, and persistent, coordinate straining on the toilet is not widely-recognized as a source of painful gynaecological symptoms though may occur in 20-30% of urban, Western populations [22]. Detailed clinical histories will identify these patterns of behaviour that may start as early as “toilet training” and become apparent, with devastating impact, at menarche [23]. The simplest way to confirm this relationship is to ask teenage girls with chronic pelvic pain three precise questions; (i) how are your bowels? (ii) how often do you go to the toilet once per day, once per week, once per month? (iii) do you have to strain to start or finish? The option of “once per month” allows the teenage girl to admit to “once per week” without any distress or embarrassment. That is usually consistent with prolonged, physical efforts during defaecation, abbreviated to “straining on the toilet” that creates specific neuro-immunohistochemical signatures [23,24], (**Figure 2D**).

The uterosacral ligaments meet in a smooth, crescentic, U-shape behind the uterus [25,26], (**Figure 4A**). On many occasions they are thickened (prolonged straining on the toilet or in the second stage of labour), thinned (hyperstimulated with oxytocin, prostaglandins or misoprostol), scarred (intrapartum or surgical injuries), or, completely absent (avulsed during evacuatory uterine procedures, common in China but not US/UK, (**Figures 4A–4F**). If there is any continuity of the substance of the uterosacral ligaments and the uterus then aberrant reinnervation and chronic pelvic pain are potential sequelae [15]. Other gynaecological procedures requiring a vulsellum may carry similar consequences e.g. laparoscopy, LEEP, cone biopsy, etc. Clearly, careful re-evaluation of the potential impacts of gynaecological surgery on pelvic neuroanatomy may be appropriate to prevent injury to the woman.

Consequences of Injuries to Pelvic Autonomic Nerves

Typically, there is a smooth, nerve plexus between the endometrium and the myometrium [13], (**Figure 2A**) though traumatic neural injuries result in collateral sprouting of nerve bundles (**Figure 2B**) and widespread stromal reinnervation

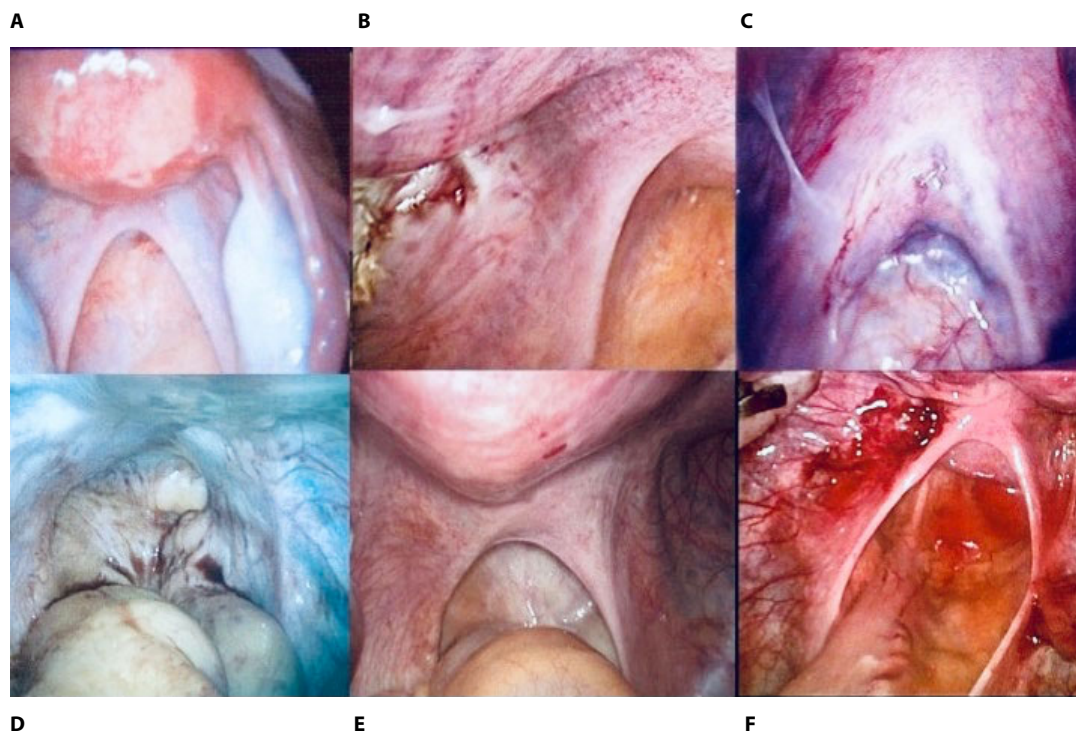


Figure 4. Injuries to the uterosacral ligaments. **A.** Normal uterosacral ligaments (USL) conduct uterine and tubal nerves to the subserosal and endometrial-myometrial nerve plexi. **B.** Minor scarring to the left USL illuminated by a deposit of ectopic endometrium. These minor injuries during evacuation of the uterus may contribute to remote development of myomas [27,28]. **C.** Thickened USL caused by prolonged and persistent, coordinate straining at stool may result in aberrant reinnervation, chronic pelvic pain and retrograde menstruation [23]. **D.** Absent USL caused by recurrent medical and surgical abortion procedures contribute to development of “painless” adenomyosis. Markedly, enlarged uteri (250-1500 g) contain little, or no, detectable neurological material [26]. **E.** Marked scarring of USL leads to aberrant reinnervation in the distal insertions and bilateral, “painful” adenomyosis [25,26]. **F.** Attenuation of USL associated with administration of oxytocin, prostaglandins and misoprostol results in aberrant reinnervation and unilateral or bilateral chronic pelvic pain [25,26]. Division of both USL at hysterectomy relieves pain promptly.

(**Figure 2C**). Such injuries are, by definition, traumatic in origin and, may result from traumatic vaginal deliveries, or, gynaecological surgery, or, straining on the toilet [19]. “Longitudinal” injuries to the nerve bundles caused by straining on the toilet, or, prolonged maternal voluntary efforts in the second stage of labour, results in the typical histological appearance of perivascular nerve fibre proliferation ([19], PVNFP) that has been found in almost all pelvic organs in different, painful, gynaecological syndromes [23], (**Figure 2D**). Women have different shapes of pelvis and different patterns of straining that result in anatomically-diverse, clinical syndromes ranging from vulvodynia in the anterior pelvis to rectal hypersensitivity in the posterior pelvis [24]. The range of pathophysiological consequences of neurological injury are shown in (**Table 1**).

The Gynaecological Syndromes

Many painful, gynaecological syndromes are associated with different patterns of neurological injury e.g. vulvodynia, dyspareunia, chronic pelvic pain, irritative bladder and

bowel syndromes, interstitial cystitis, etc. [2,7,19], (**Figure 2**). All of these syndromes have been shown to be associated with neurological injury by different authors in different clinical contexts. These may best be interpreted as “pain or discomfort in response to light touch” (technically these are different patterns of visceral allodynia) where direct touch, or, dilating blood vessels in the second half of the menstrual cycle, create different, “premenstrual” pain syndromes [19,23], (**Figure 2D**). Reducing pelvic blood flow with oral contraceptive preparations, levonorgestrel-IUS, GnRH agonists, oophorectomy, menopause etc. may be helpful.

Endometriosis, Adenomyosis, and Leiomyoma

These three, specific, gynaecological pathologies frequently coexist because they result from injuries to pelvic nerves at different anatomical sites en route, or within, the uterus [27], (**Figures 2A–2D, Figures 4A–4D**) Savitskii [28] described myometrial denervation in many forms of myoma in the early 1980’s. The clinical and histological differences between “painful” and “painless” adenomyosis may be helpful in

understanding their pathoanatomy [26]. In a series of 31 nulliparous women with one- to three prior abortions, undergoing hysterectomy in their 40's for uteri weighing 250-1160 g, the uterosacral ligaments were completely avulsed (**Figure 4D**), and, there were few, if any, nerves in the uterus and fallopian tubes [26]. In a second series of 16 women undergoing hysterectomy for unilateral, or bilateral, chronic pelvic pain; there was unilateral, or bilateral, scarring of the ipsilateral uterosacral ligament with aberrant reinnervation within the insertion of the ligament or adjacent myometrium [26], (**Figures 4B and 4D**). Division of the uterosacral ligaments relieves the pain immediately. So, complete avulsion of the uterine nerve supply, including the endometrial-myometrial nerve plexus, produces hyperplasia of both endometrium and myometrium producing "painless" adenomyosis (**Figure 4B**). Partial injury to the uterosacral ligaments and their contained nerves, also clearly impairs the endometrial-myometrial nerve plexus enabling endometrium to invade the myometrium (**Figure 4E**).

Several groups have drawn attention to injuries to pelvic nerves in "endometriosis" [8,29–31], (**Figure 5**) though many clinicians continue to manage women with chronic pelvic pain according to the 1922 observations by John Sampson that

attribute symptoms to deposits of ectopic endometrium ([32], 'the 1922 narrative') rather than injuries to pelvic autonomic nerves ("the 2022 narrative" [33–35]). More recently our group has demonstrated that denervation of the interstitial myometrium adjacent to the Fallopian tube, is the likely source of retrograde menstruation [36], (**Figures 4C–4F**). It follows from the pathoanatomy of this injury that fertility will be impaired, and, chronic pelvic pain may result from reinnervation of the uterus [36]. The distinctive pathological feature and clinical presentations of "endometriosis" may result from a single denervatory pathophysiology with deposits of ectopic endometrium simply adhering to anatomic sites of tissue injury ("the 2022 narrative", [35]). Excision or ablation of the overlying ectopic endometrium may not alter the underlying injured nerves ("the 1922 narrative" [32]).

The Obstetric Syndromes

In an important collation of clinical evidence, Brosens & Romero [6] found that many of the "great" obstetric syndromes were associated with the histological finding of narrowed uterine arterioles, without articulating that these may result from injuries to adjacent uterine nerves [7,38]. Such neurovascular injuries have many diverse and varied, clinical consequences

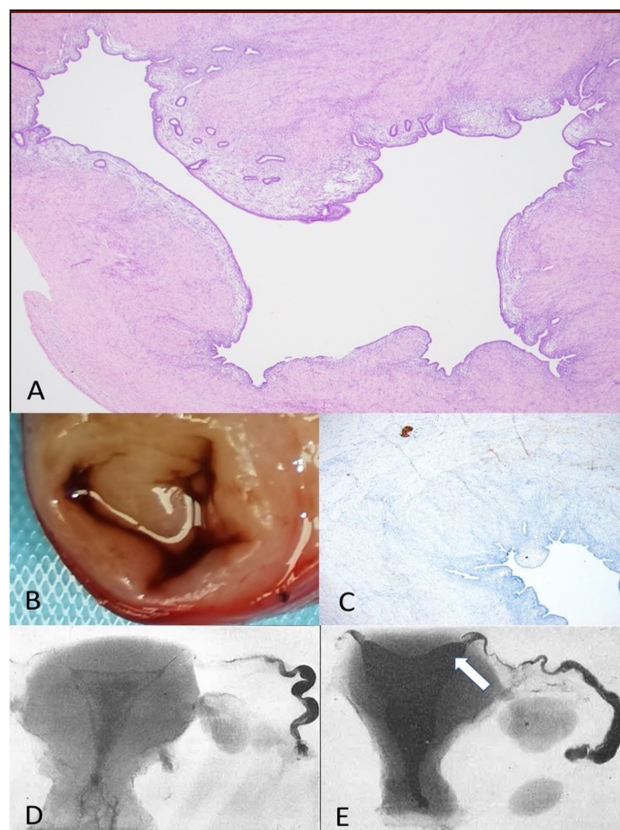


Figure 5. Retrograde menstruation, infertility and chronic pelvic pain in "endometriosis". A. Dilated interstitial fallopian tube (stained with haematoxylin and eosin, x10). **B.** Dilated, interstitial fallopian tube. **C.** Loss of nerve bundles (brown) in interstitial myometrium [36]. **D.** Normal barium hystrogram [32]. **E.** Dilated, interstitial fallopian tube [32].

to produce the clinical obstetric syndromes (**Table 1**). Injured uterine nerves may induce purinergic, P2X3, “stretch” receptors in arterioles and myometrium in preeclampsia, may weaken arterial integrity (placental abruption), increase susceptibility to “opportunistic” infection (preterm labour, preterm PROM), etc. Parous, obstetric pain syndromes, often labelled as “symphysis pubis dysfunction”, are frequently associated with injuries to uterosacral ligaments and levator avulsion syndromes, that may also be associated with denervation-reinnervation sequences following “difficult” first labours [39]. The pain is largely intractable during the pregnancy and may lead to chronic pelvic pain in the postpartum period [39].

Other Chronic Diseases

Two, data-driven hypotheses emerged in the second half of the twentieth century to explain chronic diseases; DP Burkitt’s “dietary-fibre” hypothesis and DP Barker’s “foetal origins of adult diseases” hypothesis [40,41]). Both have novel, though simple, explanations based on autonomic injury. Burkitt’s observations of reduced oro-anal transit times and increased stool weights in African (v European) populations simply reflect differences in unrefined fibre intake, which taken together with the sitting (v squatting) position for defaecation leads to marked increases in physical efforts during defaecation that result in characteristic injuries to autonomic nerves [40], (**Figure 2D**). It is not easy for humans to strain effectively in the squatting position. If the physical efforts are coordinate then they tend to injure pelvic sympathetic segments (T10-L2) and branches of parasympathetic segments with characteristic

histological lesions; if they are, hypothetically, “incoordinate” (dyssynergic) then they may injure higher sympathetic segments and branches of the vagus nerves in the thorax and abdomen [24] to produce chronic diseases with known neuropathic lesions e.g. appendicitis [42], Crohn’s disease [43], ulcerative colitis [44], diverticulosis [45] etc. Similar injuries may result from prolonged physical efforts in the second stage of labour and result in vulvodynia, dyspareunia, chronic pelvic pain, irritative bladder and bowel syndromes, etc. after varying latent periods in the respective tissues [23].

DP Barker’s “foetal origins of adult diseases” may have been uncovered in a small series of poorly-grown (<1stcentile), mid-trimester stillbirths where examination of the viscera show widespread autonomic injury with narrowed arterioles, similar to that seen in essential hypertension [46,47]. The prevailing hypothesis for this pattern of “foetal hypertension” is that involuntary transmission of mediators of stress may cross the placenta to cause these visceral injuries in the foetus [48]. Previously labelled as “congenital” conditions, these autonomic injuries may further progress if the child has difficulties with establishing a smooth, regular, bowel habit.

Hypertension

Hypertension is a lifelong condition that may originate in utero (foetal hypertension), adopt different mechanisms during pregnancy (pregnancy hypertension, or, pre-eclampsia), or develop in later life (essential hypertension) owing to mechanical disruption of sympathetic vasomotor nerves by

Table 1. Diverse, and varied, consequences of injuries to autonomic nerves.
1) Tissue hyperplasia. Endometrial hyperplasia (myoma), myometrial hyperplasia (adenomyosis), cervical hyperplasia are consequences of oestrogen-dependent hyperplasia [28].
2) Tissue hypoplasia. In non-oestrogen-dependent tissues there is atrophy of denervated tissues e.g. bladder, bowel, vagina, vulva, etc. (**)
3) Loss of visceral function. Early pregnancy loss, loss of cervical function in labour (cervix will not dilate), or at hysteroscopy (cervix will not open easily) [16].
4) Loss of visceral motility. Dyspolar uterine and tubal motility leads to infertility, retrograde menstruation, and, dysfunctional labour [56].
5) Opportunist infection. <i>E. coli</i> in preterm labour, vulvovaginal Candidiasis, bacterial vaginosis in gynaecology [57].
6) Pain. Reinnervation leads to “pain in response to light touch” (hyperalgesia or allodynia) e.g. dysmenorrhea, vulval pain, uterosacral pain, “mesh” pain, etc. [58].
7) CNS sensitization. Interstitial cystitis, chronic pain syndromes, postmenopausal pain, chronic vulval pain, etc. or neurovascular reflexes in migraine and the menopause [58].
8) Induction of “new” receptors e.g. purinergic, P2X3, “stretch” receptors, vascular epithelial growth factor (VEGF), TRPV-1, etc. as secondary mechanisms of intercellular communication [53,54].
9) Viscero-visceral reflexes. The uterorenal reflex may lead to activation of a corticomedullary vascular “shunt” in pre-eclampsia. Wider activation of the autonomic nervous system including headache, migraines, nausea, vomiting, restlessness, fatigue, etc. may also take place in chronic pelvic pain with, or without, “endometriosis” [59].
10) Ischemia-thrombosis. Injuries to visceral vasomotor nerves cause narrowing of arterioles through secondary hyperplasia of the denervated arteriole. Pregnancy complications including placental abruption and placental infarction are associated with narrowing of visceral arterioles [60].

high intravascular pressures resulting from excessive stress, sugar, salt, smoking, etc. [49,50]. Narrowing of renal, splenic, pancreatic and adrenal arterioles was originally described in 1937 by Moritz & Oldt, Case Western University, in a detailed histological analysis of 100 hypertensive postmortems where they found narrowed arterioles in kidney, spleen, pancreas, and adrenals [9] though not the adjacent injured vasomotor nerves [49,50].

Many hypotheses have been advanced to explain pre-eclampsia. The "uterine stretch" hypothesis was first articulated by Otto Spiegelburg in 1878 [51]; it requires an afferent intrauterine mechanism with neural connections between the uterus and kidneys. GJ Sophian's animal experiments in the 1950's provided direct evidence for uterorenal "reflexes" in rabbits [52]. The finding of "new", P2X3, "stretch" receptors in uterine arterioles ("early-onset" preeclampsia) and myometrium ("late-onset" preeclampsia), may be helpful in promoting this view of the condition (**Figures 1C and 1D**), [53,54]. Most clinicians will agree that delivery of the baby ("release of stretch") relieves a woman of the clinical syndrome. Absolute proof of these findings in preeclamptic uteri may not be possible with contemporary technology, though the "uterine stretch" hypothesis looks like a reasonable explanation of most features of the clinical syndrome. Sustained hypertension during pregnancy is clearly unhelpful to an individual woman at high blood pressures will lead to injuries to sympathetic vasomotor nerves, narrowing of adjacent arterioles, and, increases her chances of developing chronic hypertension in later life [55].

Conclusions

Many of the "great" obstetric and gynaecological syndromes show clear histological evidence of neurovascular injuries in the form of narrowed arterioles with associated injured nerves (gynaecological syndromes), or, injured nerve sheaths (obstetric syndromes). Injuries to uterine nerves result from a small number of preventable injuries including (i) coordinate and incoordinate, straining on the toilet, (ii) "difficult" first labours that are prolonged, or, "complex", (iii) some forms of "neuropathic", gynaecological surgery. They produce a wide range of diverse, and varied, clinical consequences that we recognize as different obstetric and gynaecological syndromes, and, chronic diseases. The denervation-reinnervation sequences takes place over a number of years in one or more adjacent viscera, with their timescales that vary in different tissues, and, may be further delayed by intervening vaginal deliveries. Selective injuries to autonomic nerves during embalming procedures in undergraduate medical education, and, variable latent periods for reinnervation in different tissues, may have obscured their origins.

Most obstetric and gynaecological syndromes are preventable. Preventive measures include neuroprotective

intrapartum, and, surgical care with more liberal use of Caesarean section and thoughtful surgical techniques that avoid neuropathic injuries. Impaired bowel habits require specific advice to diet and bowel habits to prevent neuropathic injuries in the abdomen and pelvis. In 1993, DP Burkitt said "we will waste three or four decades in pursuing complex (genomic) explanations of disease before returning to simple, lifestyle, explanations". Three decades after Burkitt's admonition, there are few signs of significant changes in clinical, or research, policy. On this evidence, much of women's reproductive ill-health may be preventable by simple, neuroprotective measures that avoid intrapartum, surgical and defecatory injuries.

Bilateral swathes of postganglionic sympathetic, autonomic nerves from T10-L2 pass through the uterosacral -cardinal ligament complex to converge on the vaginal vault. Sacral parasympathetic fibres (S2-4) emerge from sacral foramina to merge with them in the pelvic plexi. This specimen was prosected in alcohol, rather than formalin, since the latter selectively destroys these nerves [12]. They are vulnerable to injury in labour, during gynaecological surgery, and, through straining on the toilet [19,23].

Conflicts of Interest

There are no conflicts of interest associated with this manuscript. All clinical studies cited in this manuscript were carried out with the express permission of the local research ethics committees in UK and China.

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